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RESEARCH ARTICLE

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Polygenic prediction of the risk of perinatal depressive symptoms

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Abstract

Background: Perinatal depression carries adverse effects on maternal health and child development, but genetic underpinnings remain unclear. We investigated the polygenic risk of perinatal depressive symptoms.

Methods: About 742 women from the prospective Prediction and Prevention of Pre-eclampsia and Intrauterine Growth Restriction cohort were genotyped and completed the Center for Epidemiologic Studies Depression scale 14 times during the prenatal period and twice up to 12 months postpartum. Polygenic risk scores for major depressive disorder, bipolar disorder, schizophrenia, and cross-disorder were calculated using multiple *p*-value thresholds.

Results: Polygenic risk scores for major depressive disorder, schizophrenia, and cross-disorder, but not bipolar disorder, were associated with higher prenatal and postpartum depressive symptoms (0.8%–1% increase per one standard deviation increase in polygenic risk scores). Prenatal depressive symptoms accounted for and mediated the associations between the polygenic risk scores and postpartum depressive symptoms (effect size proportions-mediated: 52.2%–88.0%). Further, the polygenic risk scores were associated with 1.24–1.45-fold odds to belong to the

group displaying consistently high compared with consistently low depressive symptoms through out the prenatal and postpartum periods.

Conclusions: Polygenic risk scores for major depressive disorder, schizophrenia, and cross-disorder in non-perinatal populations generalize to perinatal depressive symptoms and may afford to identify women for timely preventive interventions.

KEYWORDS

depression, epidemiology, genetics, mood disorders, pregnancy and postpartum

1 | INTRODUCTION

Maternal perinatal depression, defined as depression during pregnancy or within 12 months of childbirth, affects over 1 of 10 women in childbearing age (World Health Organizaton, 2015). Reported clinically relevant symptoms are even more common, affecting 1 of 5 women (Kumpulainen et al., 2018; Lahti et al., 2017). It causes a major burden on the health and well-being of the women and is associated with problems such as gestational diabetes and hypertension in pregnancy (Bansil et al., 2009) and obesity (Kumpulainen et al., 2018). It is also a major risk factor of suicide, one of the most common causes of death among women during the perinatal period (Chang, Berg, Saltzman, & Herndon, 2005; Nock et al., 2008). In addition to the women themselves, perinatal depression affects their children: prenatal depression is associated with developmental adversities, including increased risk of low birth weight and preterm birth (Pesonen et al., 2016). Both prenatal and postpartum depression (PPD) are associated with lower rates and shorter duration of breastfeeding (Figueiredo, Canário, & Field, 2014), less secure mother-child attachment (Martins & Gaffan, 2000), and higher risk of child neurodevelopmental, emotional, and behavioral problems (Lahti et al., 2017; Toffol et al., 2019; Tuovinen et al., 2018; Wolford et al., 2017).

While the risk of perinatal depression is modified by psychosocial (Yim, Tanner Stapleton, Guardino, Hahn-Holbrook, & Dunkel Schetter, 2015) and hormonal (Schiller, Meltzer-Brody, & Rubinow, 2015) factors, twin (Treloar, Martin, Bucholz, Madden, & Heath, 1999; Viktorin et al., 2016), sibling (Murphy-Eberenz et al., 2006; Viktorin et al., 2016) and family (Forty et al., 2006; Pearson et al., 2018) studies indicate that heritable factors also play a part. Heritability estimates of perinatal depression have varied between 25% (Treloar et al., 1999) and 54% (Viktorin et al., 2016) in twin studies, and 44% (Viktorin et al., 2016) in a sibling study. Furthermore, the daughters of prenatally depressed women have over the threefold risk of depression during their own pregnancy (Pearson et al., 2018). While perinatal depression and nonperinatal major depressive disorder (MDD) may represent at least partly distinct disorders, perinatal depression at least partially shares its genetic component with MDD (Viktorin et al., 2016) and bipolar disorder (BD; Payne et al., 2008). Moreover, the genetic component may also be shared with schizophrenia (SCZ), anorexia nervosa, attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorder (ASD), obsessive–compulsive disorder (OCD) and Tourette syndrome, due to the partially shared heritability between MDD and these disorders (Lee et al., 2013; Lee et al., 2019). Furthermore, candidate gene studies have linked single nucleotide polymorphisms (SNPs) with the risk of these disorders. However, it is unlikely that the heritabilities of these complex disorders are assigned to individual SNPs. Indeed, a recent meta-analysis concluded that no candidate genes or gene sets reliably predict depression phenotypes (Border et al., 2019).

A promising alternative is the polygenic risk score (PRS) approach, which exploits findings from genome-wide association studies (GWAS) using an aggregate measure of weighted genetic variants associated with the phenotype. One study showed that PRSs for BD, but not MDD, were associated with postpartum depression (Byrne et al., 2014). However, the study used polygenic profile scoring methodology instead of association analysis and exploited summary statistics from an older GWAS. In addition, to our best knowledge, no PRS study has sufficiently accounted for the other risk factors of perinatal depression and have focused only on PPD. However, women suffering from PPD often have elevated depressive symptoms already during early pregnancy (Evans et al., 2012; Kumpulainen et al., 2018; Tuovinen et al., 2018; van der Waerden et al., 2017), indicating that PPD is often a continuation of prenatal depression.

Accordingly, we investigated PRSs based on the most recent and largest GWAS on MDD (Howard et al., 2019; Wray et al., 2018), BD (Ruderfer et al., 2018; Stahl et al., 2019), SCZ (Ripke, Neale, & Spiker, 2014; Ruderfer et al., 2018) and cross-disorder (CD; including MDD, BD, SCZ, anorexia nervosa, ADHD, ASD, OCD, and Tourette syndrome; Lee et al., 2019) (a) predict prenatal and postpartum depressive symptoms, (b) if prenatal depressive symptoms account for, and hence mediate, or (c) moderate the associations of the PRSs and postpartum depressive symptoms, and (d) if these PRSs predict fluctuating or consistently high levels of depressive symptoms throughout the perinatal period.

2 | MATERIALS AND METHODS

2.1 | Participants

The participants come from the Prediction and Prevention of Pre-eclampsia and Intrauterine Growth Restriction (PREDO) study (Girchenko et al., 2017). We enrolled 1,079 pregnant women to the clinical subsample: 969 had one or more, and 110 had none of the known risk factors for pre-eclampsia and intrauterine growth restriction.

The women were recruited on their first ultrasound screening at 12–14 gestational weeks from 10 hospitals in Southern and Eastern the 1,079 women, 997 donated blood for DNA in early pregnancy (median = 13.0; interquartile range = 12.6–13.4 weeks). Of them, 742 (74.4%) had data available on prenatal or postpartum depressive symptoms; these women formed our analytic sample. Of them, data were available on prenatal depressive symptoms for 721 (97.2%), postpartum depressive symptoms for 726 (97.8%), and both for 705 (95.0%).

Compared with the rest of the clinical subsample, the women in the analytic sample more often had attained tertiary education (42.7% vs. 55.0%; $\chi^2 = 15.29$; $p < .001$), but did not significantly differ otherwise.

2.2 | Ethics statement

All participants signed informed consent forms. The PREDO study protocol has been approved by the ethical committee of the Helsinki and Uusimaa Hospital District, and aligns with the Declaration of Helsinki.

2.3 | Genotyping

Genotyping was performed on the IlluminaGlobal Screening array (Illumina Inc, San Diego, CA) at the Erasmus MC, The Netherlands and imputed with IMPUTE 2.3.2 and Eagle v2.3 against Finnish-specific SISu v2 reference panel (GRCh37) comprising 2690 high-coverage whole-genome and 5093 high-coverage whole-exome sequences, which introduces less false polymorphisms than using global reference panels (Surakka et al., 2016). Before imputation, variants with call rate <0.95, MAF > 0.35, minor allele count <19 or HWE $p < 1 \times 10^{-6}$ were excluded. Samples were excluded based on call rate <0.95, heterozygosity $F < 0.1$, sex mismatch, and relatedness. Population outliers were excluded based on visual inspection. There were 15,544,584 variants after imputation.

2.4 | PRS of MDD, BD, SCZ, and CD

PRS for MDD (Howard et al., 2019; Wray et al., 2018; hereafter referred to as MDD2018 and MDD2019), BD (Ruderfer et al., 2018; Stahl et al., 2019; BD2018 and BD2019), SCZ (Ripke et al., 2014; Ruderfer et al., 2018; SCZ2014 and SCZ2018), and CD (Lee et al., 2019) were calculated by taking genetic variants from the imputed best guess genotypes up to varying significance thresholds from the GWAS discovery sample and applying a score from these variants, weighted by the associations in the discovery sample, to predict a trait in an independent target sample. Clumping and calculation of PRSs were performed using PRSice-2 (Choi & O'Reilly, 2019), using LD threshold (R^2) 0.1 and clumping window width of 500 kilobases. Before clumping, we excluded all SNPs with INFO score < 0.90. Other filtering criteria in the PREDO sample included HWE $p < 1 \times 10^{-6}$ and missingness > 0.05. PRSs were created using p-value thresholds 5×10^{-8}, .001, .01, and .05. The number of SNPs in each PRS is in Table 1. The correlations between the PRSs are in Tables S1–S4.

2.5 | Depressive symptoms

The women completed the Center for Epidemiologic Studies Depression Scale (CES-D; Radloff, 1977) biweekly up to 14 times throughout the perinatal period starting from $12^{0/7}$–$13^{6/7}$ until $38^{0/7}$–$39^{6/7}$ or delivery, and twice during the postpartum period (median 2.1 weeks and 6.4 months, interquartile range 2.0–2.4 weeks and 6.1–7.3 months, respectively). The 20 CES-D questions were rated on a scale from none (0) to all of the time (3). Higher scores indicate more depressive symptoms during the past week.

2.6 | Covariates

These included age at delivery (years), family structure (cohabiting/married vs single parent), body mass index (BMI) in early pregnancy (kg/m2) and cigarette smoking (smoked through pregnancy/quit in early pregnancy vs no) with data from the Medical Birth Register. Education (secondary, tertiary vs basic) and alcohol use (yes vs no) were reported in early pregnancy. We conducted multidimensional scaling analyses on the whole genome genotypes with Plink v0.64 to control for population stratification. Four main components depicted the population substructure.

TABLE 1 Numbers of SNPs in the polygenic risk scores

p-Value threshold	MDD2018	MDD2019	BD2018	BD2019	SCZ2014	SCZ2018	CD
$p < 5 \times 10^{-8}$	48	66	8	13	118	80	134
$p < .001$	2100	2529	1263	1514	2892	2352	3251
$p < .01$	7614	9104	5618	6070	8804	7859	10190
$p < .05$	19404	23301	15730	16380	20129	18951	23562

Abbreviations: BD2018, bipolar disorder (Ruderfer et al., 2018); BD2019, bipolar disorder (Stahl et al., 2019); CD, cross-disorder; MDD2018, major depressive disorder (Wray et al., 2018); MDD2019, major depressive disorder (Howard et al., 2019); SCZ2014, schizophrenia (Ripke et al., 2014); SCZ2018, schizophrenia (Ruderfer et al., 2018).

2.7 | Statistical methods

Linear regression analyses tested the associations between the PRSs and prenatal (mean of all 14 prenatal values) and postpartum (mean of the two postpartum values) depressive symptoms. We then tested if the associations between the PRSs and postpartum depressive symptoms were accounted for by prenatal depressive symptoms, by adding prenatal depressive symptoms to the regression equations. We pursued mediation if all variables were significantly interrelated and the regression coefficient diminished after introducing the mediator into the model (Baron & Kenny, 1986). To study if prenatal depressive symptoms moderated the associations between the PRSs and postpartum depressive symptoms, we included a prenatal depressive symptoms × PRS interaction termin the regression equation together with the main effects.

Finally, to study if the PRSs were associated with fluctuating or persistently high levels of prenatal and postpartum depressive symptoms, we first applied latent class analysis (LCA) to identify subgroups of women based on their depressive symptoms levels across all measurements. We compared two to six subgroups solutions using the following criteria for the optimal solution: (a) Akaike and Bayesian Information Criteria of goodness-of-fit, (b) at least 10% of the sample in each subgroup, (c) high classification certainty identified by posterior probabilities, (d) clinical relevance (Kongsted & Nielsen, 2017), and (e) changes in log likelihoods for increasing the number of subgroups. Using multinomial and ordinal regression analyses, we then examined if the PRSs were associated with the depressive symptoms subgroups identified as optimal.

We present the associations as adjusted for the MDS and maternal age, and further for all covariates. We normalized CES-D values with square root transformation and standardized the CES-D scores and the PRSs (Mean = 0; *SD* = 1) to facilitate interpretation. Unstandardized regression coefficients and odds ratios (OR) and 95% confidence intervals (95% CI) with two-tailed *p*-values present effect sizes.

We controlled for multiple testing with a false detection rate (FDR) procedure (Benjamini & Hochberg, 1995). We corrected for 5% FDR over 28 tests (seven PRSs with four *p*-value thresholds), separately for prenatal and postpartum CES-D scores and for each statistical model.

We conducted the analyses using SPSS v24 and PROCESS macro v3.3 (Hayes, 2017) with a custom model builder (Frank, 2018) using 10,000 bootsrapped samples. We corrected for FDR using the p.adjust function in R.

2.8 | Data availability statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Data requests may be subject to further review by the Finnish national register authorities, and by the ethical committees.

3 | RESULTS

Sample characteristics are in Table 2. The CES-D scores were correlated across all 16 measurements (Pearson's $r = .40–.81$; $p < .001$). The correlation between the means of prenatal and postpartum measurements was Pearson's $r = .68$ ($p < .001$). Of the covariates, only alcohol use and early pregnancy BMI were correlated with prenatal depressive symptoms (Pearson's $r \geq .09$; $p \geq .022$), and none were correlated with postpartum depressive symptoms (Table S5).

3.1 | PRS and prenatal and postpartum depressive symptoms

Table 3 shows that the MDD2018, MDD2019, SCZ2014, SCZ2018, and CD PRSs with *p*-value threshold .01 were significantly associated with higher levels of prenatal and postpartum depressive symptoms in both statistical models adjusting for covariates, except for

TABLE 2 Sample characteristics

Characteristic	Mean (*SD*) or n (%)
Maternal age at delivery (years)	33.4 (5.6)
Missing data	0 (0.0%)
Education	
Basic	24 (3.2%)
Secondary	299 (40.3%)
Tertiary	408 (55.0%)
Missing data	11 (1.5%)
Family structure	
Married or cohabit	720 (97.0%)
Single	22 (3.0%)
Missing data	0 (0.0%)
Early pregnancy BMI (kg/m^2)	27.2 (6.7)
Missing data	0 (0.0%)
Smoking during pregnancy	
No	703 (94.7%)
Yes	38 (5.1%)
Missing data	1 (0.1%)
Alcohol use in early pregnancy	
No	609 (82.1%)
Yes	115 (15.5%)
Missing data	18 (2.4%)
CES-D	
Prenatal mean score	11.4 (6.6)
Above clinical cutoff (≥16)	152 (20.5%)
Missing data	21 (2.8%)
Postpartum mean score	10.2 (7.3)
Above clinical cutoff (≥16)	138 (18.6%)
Missing data	16 (2.2%)

Abbreviations: BMI, body mass index; CES-D, Center of Epidemiologic Studies Depression Scale; *SD*, standard deviation.

TABLE 3 Associations between standardized PRSs for MDD2018, MDD2019, SCZ2014, SCZ2018, and CD and prenatal and postpartum depressive symptoms

Prenatal depressive symptoms								Postpartum depressive symptoms							
Polygenic risk score	*p*-Threshold	Statistical model	*B*	95% CI	*p*	*p* FDR	R^2	Polygenic risk score	*p*-Threshold	Statistical model	*B*	95% CI	*p*	*p* FDR	R^2
MDD2018	$p < 5 \times 10^{-8}$	Model 1	0.09	0.01, 0.17	.022	.051	.007	MDD2018	$p < 5 \times 10^{-8}$	Model 1	0.07	−0.00, 0.15	.069	.114	.005
		Model 2	0.08	0.01, 0.16	.034	.073	.006			Model 2	0.07	−0.01, 0.15	.077	.127	.004
										Model 3	0.02	−0.04, 0.08	.496	.634	.000
	$p < .001$	Model 1	0.05	−0.02, 0.13	.165	.231	.003		$p < .001$	Model 1	0.09	0.01, 0.16	.027	.058	.007
		Model 2	0.06	−0.02, 0.13	.155	.220	.003			Model 2	0.08	0.02, 0.17	.019	.047	.008
										Model 3	0.05	−0.01, 0.11	.084	.319	.002
	p < 0.01	Model 1	0.10	0.03, 0.18	.008	.036	.010		$p < .01$	Model 1	0.12	0.04, 0.20	.002	.014	.013
		Model 2	0.10	0.03, 0.18	.009	.044	.009			Model 2	0.12	0.05, 0.20	.002	.014	.014
										Model 3	0.05	−0.01, 0.11	.091	.319	.002
	p < 0.05	Model 1	0.10	0.03, 0.18	.008	.036	.010		$p < .05$	Model 1	0.13	0.05, 0.20	.001	.014	.015
		Model 2	0.10	0.02, 0.17	.013	.044	.008			Model 2	0.13	0.05, 0.20	.001	.014	.014
										Model 3	0.05	−0.01, 0.11	.083	.319	.002
MDD2019	$p < 5 \times 10^{-8}$	Model 1	0.08	−0.00, 0.16	.058	.102	.005	MDD2019	$p < 5 \times 10^{-8}$	Model 1	0.08	−0.01, 0.16	.065	.114	.005
		Model 2	0.08	−0.00, 0.16	.058	.102	.005			Model 2	0.08	−0.00, 0.17	.052	.097	.005
										Model 3	0.04	−0.03, 0.10	.231	.462	.001
	$p < .001$	Model 1	0.06	−0.01, 0.14	.099	.163	.004		$p < .001$	Model 1	0.09	0.02, 0.17	.018	.046	.008
		Model 2	0.05	−0.02, 0.13	.157	.220	.003			Model 2	0.09	0.02, 0.17	.019	.047	.008
										Model 3	0.05	−0.01, 0.11	.109	.339	.002
	$p < .01$	Model 1	0.09	0.02, 0.17	.013	.040	.008		$p < .01$	Model 1	0.09	0.02, 0.17	.016	.045	.008
		Model 2	0.09	0.01, 0.16	.023	.059	.007			Model 2	0.09	0.01, 0.16	.022	.047	.007
										Model 3	0.01	−0.01, 0.07	.798	.828	.000
	$p < .05$	Model 1	0.10	0.02, 0.17	.009	.036	.009		$p < .05$	Model 1	0.11	0.03, 0.18	.006	.028	.010
		Model 2	0.09	0.02, 0.17	.016	.045	.008			Model 2	0.10	0.03, 0.80	.009	.035	.009
										Model 3	0.02	−0.04, 0.08	.498	.634	.000
SCZ2014	$p < 5 \times 10^{-8}$	Model 1	0.09	−0.00, 0.18	.058	.102	.005	SCZ2014	$p < 5 \times 10^{-8}$	Model 1	0.10	0.00, 0.19	.043	.086	.006
		Model 2	0.09	0.00, 0.18	.041	.077	.006			Model 2	0.10	0.01, 0.20	.030	.060	.006
										Model 3	0.03	−0.04, 0.10	.385	.599	.001
	$p < .001$	Model 1	0.12	0.04, 0.20	.004	.036	.011		$p < .001$	Model 1	0.11	0.03, 0.19	.008	.032	.010
		Model 2	0.13	0.05, 0.21	.002	.019	.013			Model 2	0.11	0.03, 0.19	.007	.033	.010
										Model 3	0.03	−0.03, 0.09	.328	.574	.001
	$p < .01$	Model 1	0.12	0.04, 0.20	.003	.036	.012		$p < .01$	Model 1	0.13	0.05, 0.21	.001	.014	.014
		Model 2	0.12	0.04, 0.20	.002	.019	.013			Model 2	0.13	0.05, 0.21	.002	.014	.014
										Model 3	0.05	−0.01, 0.11	.130	.364	.002

TABLE 3 (Continued)

Prenatal depressive symptoms								Postpartum depressive symptoms							
Polygenic risk score	*p*-Threshold	Statistical model	*B*	95% CI	*p*	*p* FDR	R^2	Polygenic risk score	*p*-Threshold	Statistical model	*B*	95% CI	*p*	*p* FDR	R^2
	$p < .05$	Model 1	0.09	0.02, 0.17	.018	.046	.008		$p < .05$	Model 1	0.10	0.02, 0.18	.014	.044	.008
		Model 2	0.10	0.02, 0.18	.012	.044	.009			Model 2	0.10	0.02, 0.18	.014	.044	.008
										Model 3	0.03	−0.03, 0.09	.288	.538	.001
SCZ2018	$p < 5 \times 10^{-8}$	Model 1	0.10	0.00, 0.19	.047	.094	.005	SCZ2018	$p < 5 \times 10^{-8}$	Model 1	0.06	−0.01, 0.16	.188	.267	.002
		Model 2	0.10	0.01, 0.20	.027	.063	.007			Model 2	0.07	−0.02, 0.17	.133	.206	.003
										Model 3	0.00	−0.07, 0.07	.995	.995	.000
	$p < .001$	Model 1	0.10	0.02, 0.18	.015	.042	.008		$p < .001$	Model 1	0.09	0.01, 0.18	.024	.056	.007
		Model 2	0.10	0.02, 0.18	.013	.044	.008			Model 2	0.10	0.02, 0.18	.020	.047	.007
										Model 3	0.02	--0.04, 0.08	.528	.643	.000
	$p < .01$	Model 1	0.12	0.04, 0.20	.003	.036	.012		$p < .01$	Model 1	0.11	0.02, 0.19	.012	.042	.009
		Model 2	0.13	0.05, 0.21	.002	.019	.013			Model 2	0.11	0.03, 0.19	.010	.035	.009
										Model 3	0.02	−0.04, 0.09	.491	.634	.000
	$p < .05$	Model 1	0.10	0.02, 0.16	.011	.039	.009		$p < .05$	Model 1	0.13	0.05, 0.21	.002	.014	.013
		Model 2	0.11	0.03, 0.18	.008	.044	.009			Model 2	0.13	0.05, 0.21	.002	.014	.013
										Model 3	0.06	−0.00, 0.12	.064	.319	.003
CD	$p < 5 \times 10^{-8}$	Model 1	0.07	−0.02, 0.16	.134	.208	.003	CD	$p < 5 \times 10^{-8}$	Model 1	0.07	−0.03, 0.16	.167	.260	.003
		Model 2	0.08	−0.02, 0.17	.106	.175	.004			Model 2	0.07	−0.02, 0.17	.140	.206	.003
										Model 3	0.03	−0.05, 0.10	.472	.634	.000
	$p < .001$	Model 1	0.06	−0.02, 0.13	.164	.231	.003		$p < .001$	Model 1	0.07	−0.00, 0.15	.062	.114	.005
		Model 2	0.06	-0.02, 0.13	.155	.220	.003			Model 2	0.08	−0.00, 0.15	.062	.109	.005
										Model 3	0.01	−0.05, 0.08	.643	.692	.000
	$p < .01$	Model 1	0.10	0.03, 0.18	.009	.036	.009		$p < .01$	Model 1	0.12	0.04, 0.19	.004	.022	.011
		Model 2	0.10	0.02, 0.17	.014	.044	.008			Model 2	0.11	0.04, 0.19	.004	.022	.011
										Model 3	0.03	−0.03, 0.09	.358	.590	.001
	$p < .05$	Model 1	0.09	0.01, 0.16	.026	.056	.007		$p < .05$	Model 1	0.05	−0.03, 0.13	.191	.267	.002
		Model 2	0.08	0.00, 0.15	.041	.077	.006			Model 2	0.05	−0.03, 0.13	.186	.260	.002
										Model 3	−0.02	−0.08, 0.04	.577	.673	.000

Abbreviations: BD, bipolar disorder; CD, cross-disorder; MDD2018, major depressive disorder (Wray et al., 2018); FDR, MDD2019, major depressive disorder (Howard et al., 2019); PRS, polygenic risk score; SCZ2014, schizophrenia (Ripke et al., 2014); SCZ2018, schizophrenia (Ruderfer et al., 2018).

Note: Model 1 adjusting for maternal age at delivery and population stratification. Model 2 adjusting for maternal age at delivery, education, family structure, body mass index, smoking, alcohol use, and population stratification. Model 3 adjusting for prenatal depressive symptoms, maternal age at delivery, education, family structure, body mass index, smoking, alcohol use, and population stratification. B, unstandardized regression coefficient; R^2, the proportion of variance in depressive symptoms explained by the PRS alone.

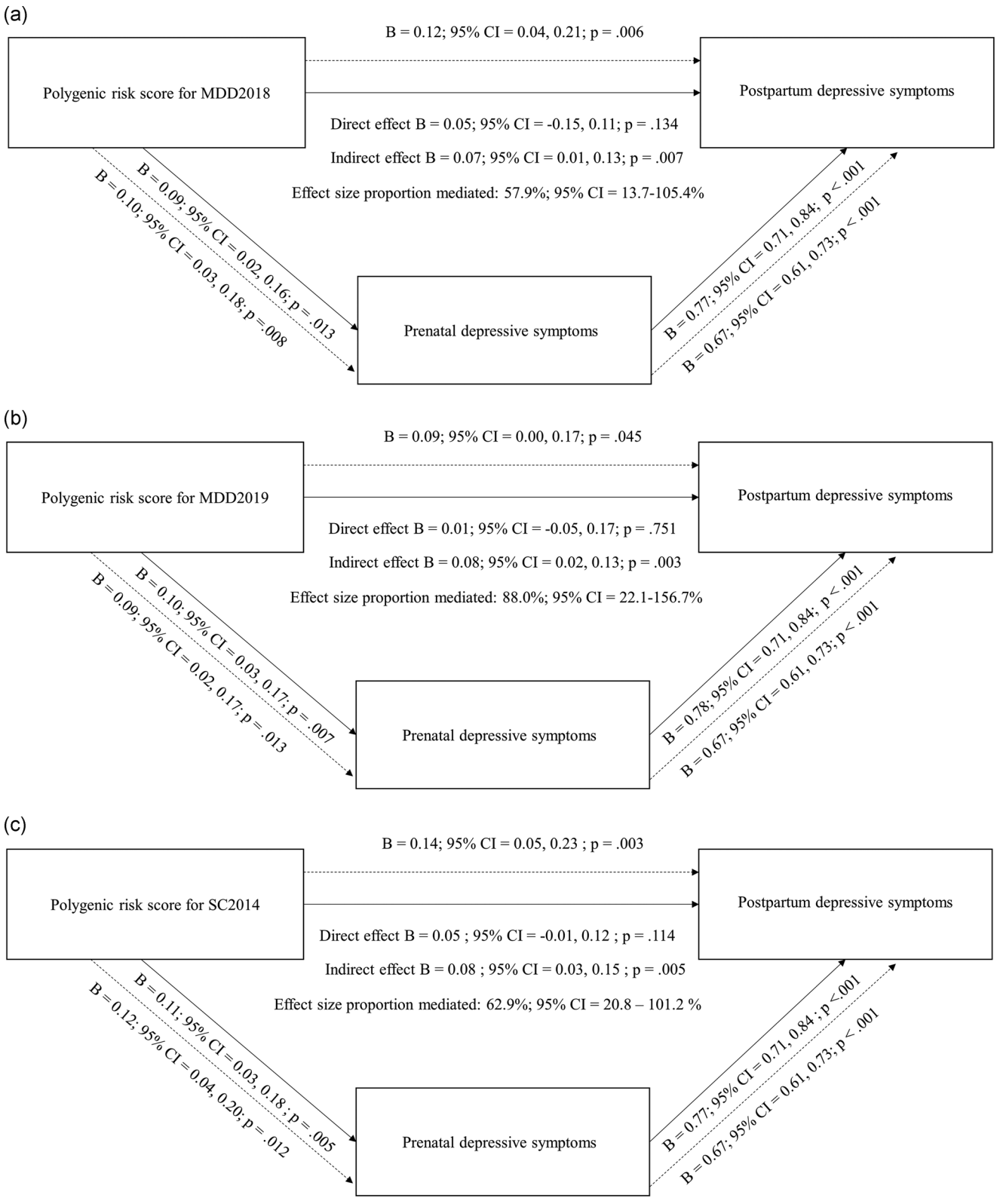

FIGURE 1 Mediation of the association between polygenic risk scores and postpartum depressive symptoms by prenatal depressive symptoms. The association between polygenic risk scores of MDD2018 (a), MDD2019 (b), SCZ2014 (c), SCZ2018 (d), and CD (e), and postpartum depressive symptoms is mediated by prenatal depressive symptoms. The*p*-values and regression coefficients shown are for the PRSs calculated using the *p*-value threshold $p < .01$, and adjusted for maternal age at delivery and population stratification. *p*-Values for indirect effects are from Sobel's test. PRS, polygenic risk score

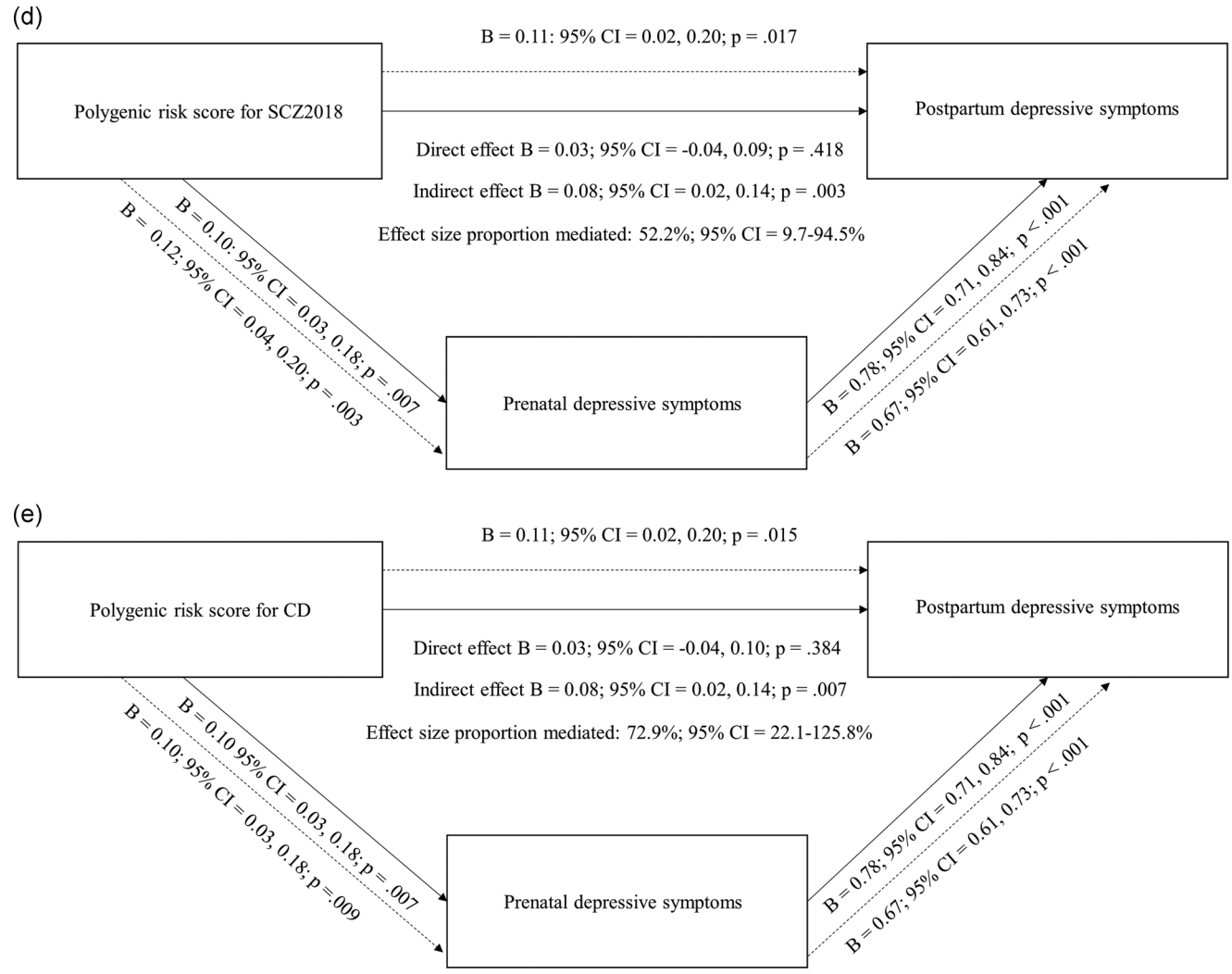

FIGURE 1 (Continued)

MDD2019, which was not associated with prenatal depressive symptoms in the fully adjusted model. The associations were similar but less consistent with the other *p*-value thresholds (Table 3). The PRSs for BD were not associated with prenatal or postpartum depressive symptoms (Table S6).

The proportion of variance explained by the entire statistical models varied between 1.3% and 6.2% for prenatal and 1.5–5.9% for postpartum depressive symptoms; R^{2}'s of the PRSs alone are in Table 3. To further characterize the polygenic basis of perinatal depressive symptoms, we conducted stepwise linear regression analyses where we first entered Model 1 covariates and then tested using forward selection which of the PRSs with *p*-value threshold 0.01 improved model fit the most. The PRSs for SCZ2018 and SCZ2014 were the best predictors of prenatal and postpartum depressive symptoms, respectively, and MDD2018 significantly predicted additional variance in prenatal and postpartum depressive symptoms: for adding the second PRS, R^2 changes were .7% and 1.0%, *F*'s for change 5.20 and 7.14, and $p = .02$ and $p = .008$, respectively.

3.2 | PRS and prenatal and postpartum depressive symptoms: Mediation and moderation

No PRSs were significantly associated with postpartum depressive symptoms in models including prenatal depressive symptoms (Table 3; Table S6). As the criteria were met (Table 3 and significant correlations between prenatal and postpartum depressive symptoms), we pursued mediation tests. Prenatal depressive symptoms mediated the associations between the PRSs for MDD2018, MDD2019, SCZ2014, SCZ2018, and CD and postpartum depressive symptoms (effect size proportions mediated varied between 52.2% and 88.0%; Figure 1). After accounting for mediation, the direct effects of the PRSs for MDD2018, SCZ2014, and SCZ2018 remained significant, but MDD2019 and CD did not (Figure 1).

Analyses testing if prenatal depressive symptoms moderated the associations between the PRSs and postpartum depressive symptoms revealed no significant interactions (prenatal depressive symptoms × PRS interactions $p \geq .152$; data not shown).

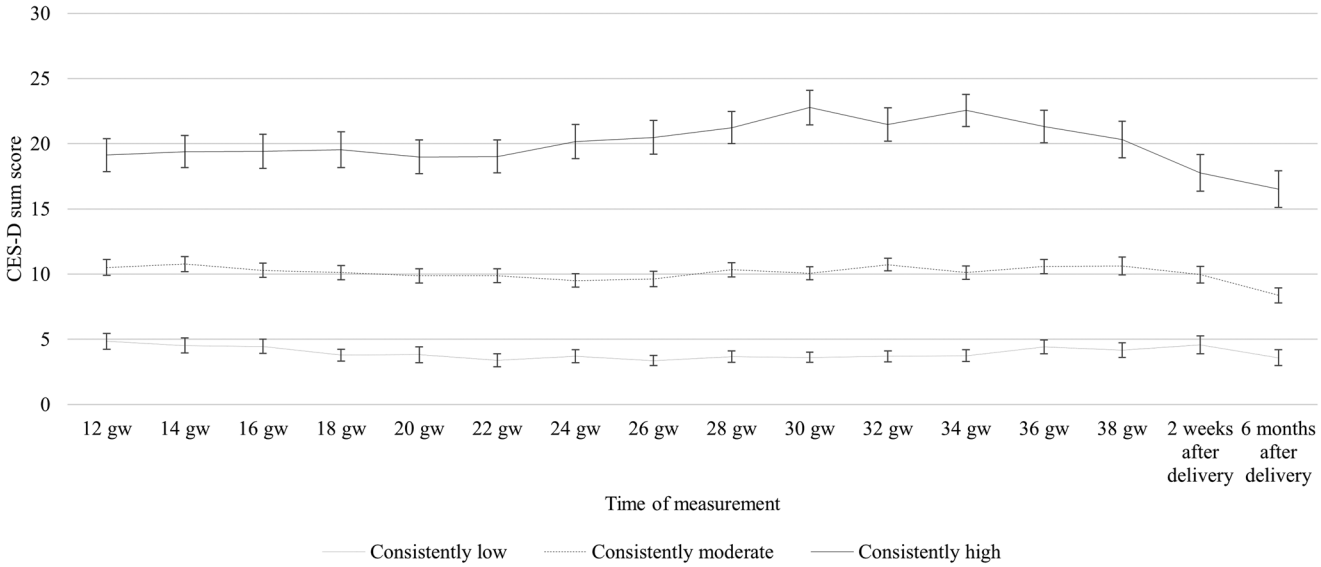

FIGURE 2 Latent profiles of maternal prenatal and postpartum depressive symptoms. The figure shows the mean levels of depressive symptoms in the three classes derived from latent class analysis of women who showed consistently low, consistently moderate and consistently high levels of depressive symptoms throughout pregnancy and up to 12 months after delivery. Error bars represent 95% CI's

3.3 | PRS and prenatal and postpartum depressive symptoms: Fluctuating or persistently high level of symptomatology

In the LCA we compared two to six subgroups solutions, and based on the five criteria identified a solution with three latent classes as optimal (Table S7). Each of the three subgroups showed high depressive symptom stability throughout the prenatal and postpartum periods (Figure 2). The groups differed in symptom severity, showing consistently low (n = 158; 21.3%), moderate (n = 397; 53.5%) and high, clinically significant (CES-D scores ≥ 16; Radloff, 1977; n = 187; 25.2%) levels of depressive symptoms.

Figure 3 shows that for each SD increase in the PRSs for MDD2018, MDD2019, SCZ2014, SCZ2018, and CD with p-value threshold .01 and for each SD increase in PRSs for MDD2018, SCZ2018, and CD with p-value threshold .05, the odds to belong to the group with consistently high compared with low depressive symptoms throughout the prenatal and postpartum periods were significantly higher (OR = 1.24–1.45). The PRSs for CD and SCZ2014 at 0.01 and 0.05 p-value thresholds were also associated with significantly higher odds (OR = 1.23–1.29) to belong to the group with consistently moderate compared with low depressive symptoms (Figure 3). The odds to belong to the LCA subgroups with consistently low, moderate, and high levels of depressive symptoms increased linearly with higher values of the PRSs (Figure 3). Figure 3 also shows the means of the PRSs according to the LCA subgroups.

The PRSs for BD2018 and BD2019 were not significantly associated with the LCA subgroups.

4 | DISCUSSION

We found that the PRSs for MDD2018, MDD2019, SCZ2014, and SCZ2018 and CD, but not BD2018 or BD2019, predicted higher levels of prenatal and postpartum depressive symptoms. While all the PRSs were correlated, only MDD2018, SCZ2014, and SCZ2018 significantly predicted unique variance in depressive symptoms. The associations were significant across PRSs calculated using multiple p-value thresholds, but they were most consistent with the PRSs containing larger numbers of SNPs. This is likely related to the genetic variance reflected in the different PRSs, as the numbers of SNPs differ widely between different p-value thresholds (Table 1). These findings thus suggest that the genetic risk of MDD, SCZ, and CD in nonperinatal populations may generalize to depressive symptoms in perinatal women.

The effect sizes that predicted prenatal and postpartum depressive symptoms were small, but of similar magnitude as those of the covariates (Table S5). Moreover, as previously reported (Evans et al., 2012; Kumpulainen et al., 2018; Tuovinen et al., 2018; van der Waerden et al., 2017), the best predictor of postpartum depressive symptomatology was prenatal symptomatology.

However, the effect size estimates were much larger when we took into account the high stability of depressive symptoms throughout the perinatal period. Our LCA indicated that the PRSs for MDD2018, MDD2019, SCZ2014, SCZ2018, and CD were associated with a trajectory of consistently high depressive symptoms across the perinatal period; one SD increase in these PRSs translated to 1.24–1.45 increase in the odds to belong to the group with consistently high compared with low depressive symptoms. Thus, genetic

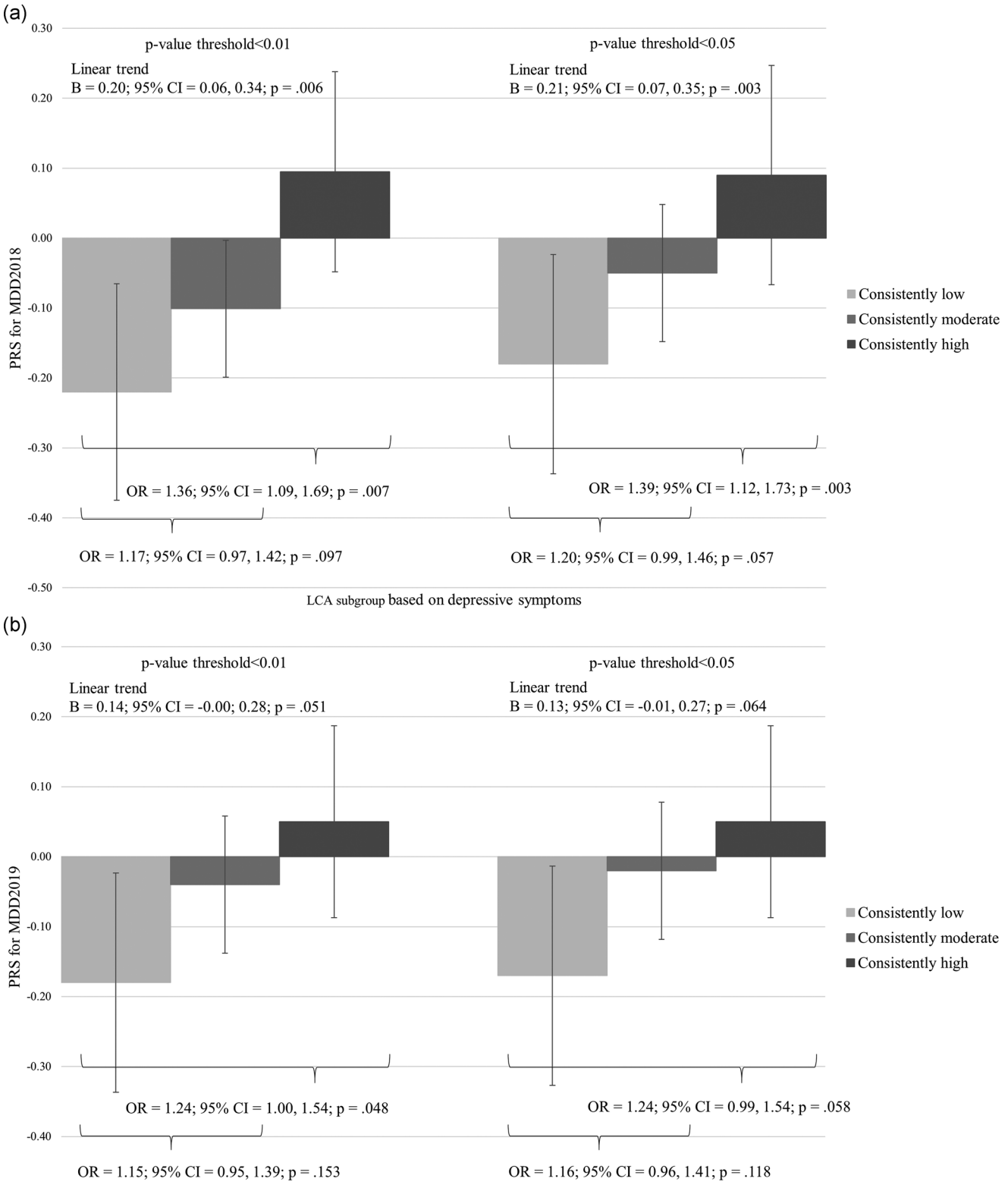

FIGURE 3 Polygenic risk for MDD2018, MDD2019, SCZ2014, SCZ2018, and CD by the three latent class analysis subgroups of perinatal depressive symptoms. PRSs for MDD2018 (a), MDD2019 (b), SCZ2014 (c), SCZ2018 (d), and CD (e) calculated using *p*-value thresholds .01 and .05 by the three latent class analysis subgroups of women with consistently low, consistently moderate and consistently high levels of depressive symptoms throughout pregnancy and up to 12 months after delivery. Error bars represent 95% CI's. Odds ratios for subgroup membership and linear trends across subgroups are adjusted for maternal age at delivery and population stratification. PRS, polygenic risk score

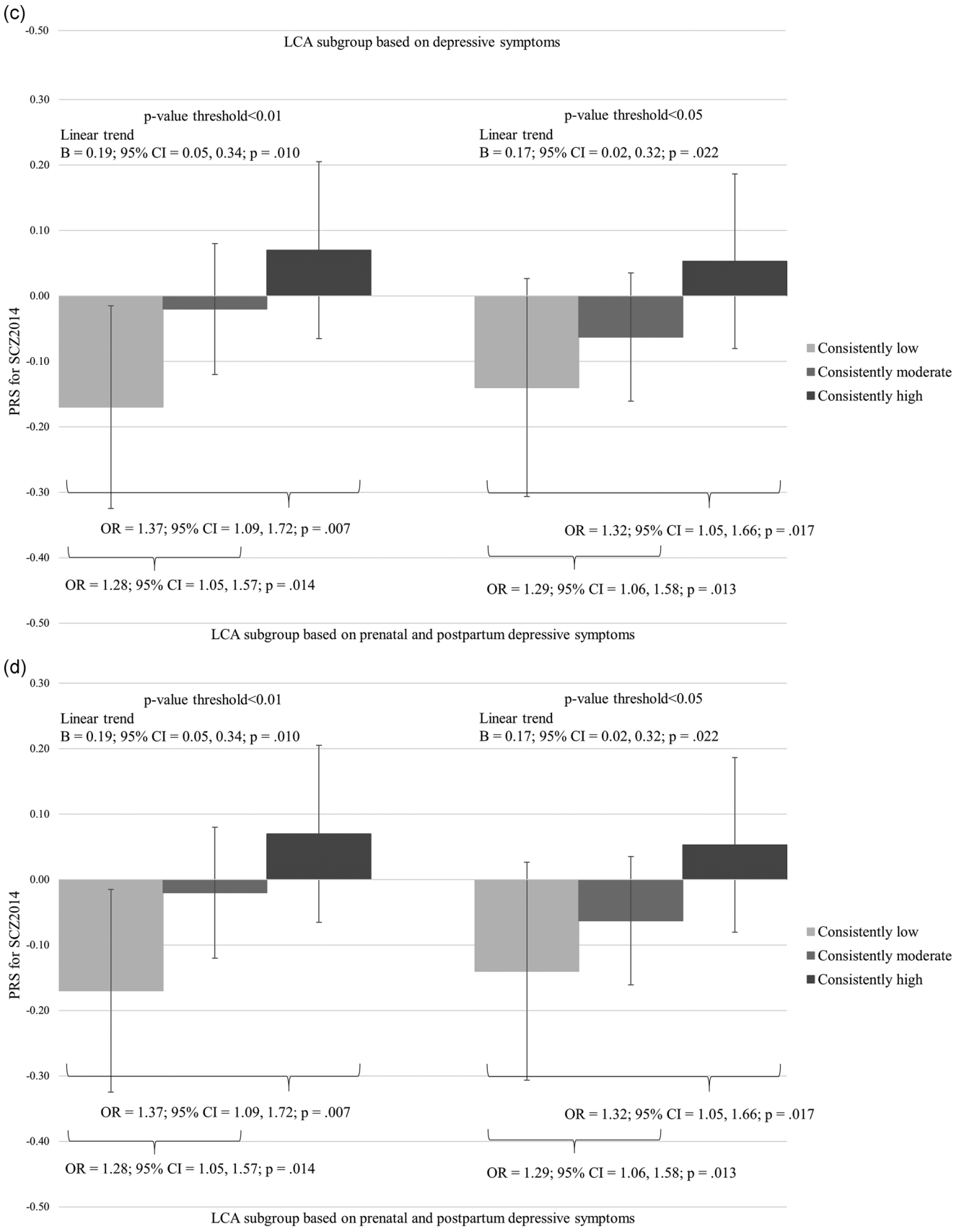

FIGURE 3 (Continued)

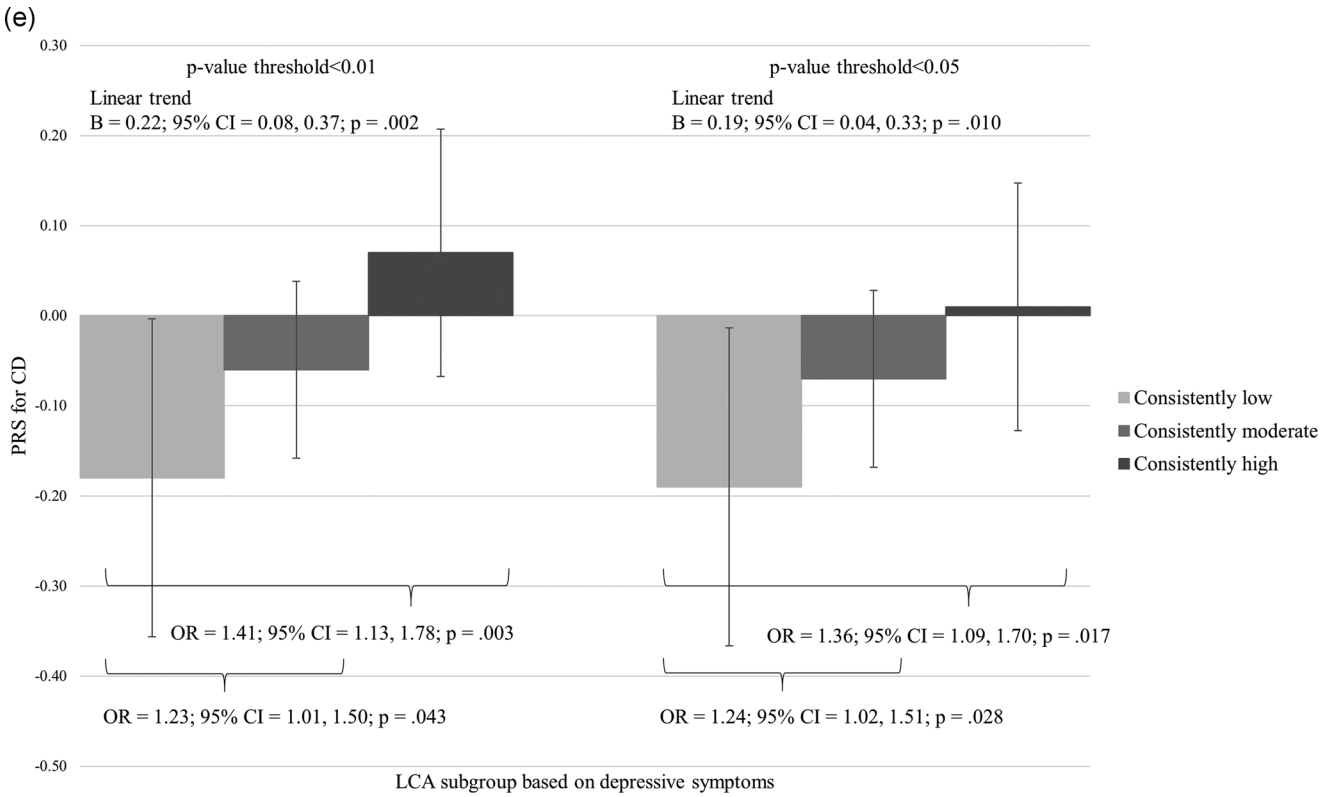

FIGURE 3 (Continued)

vulnerability may be present in a larger proportion of women suffering from consistently high levels of depressive symptoms throughout the perinatal period.

Because of this high correlation between prenatal and postpartum depressive symptomatology, the associations between the PRSs and postpartum symptomatology were rendered nonsignificant when prenatal symptomatology was introduced into the model. Indeed, the associations with postpartum depressive symptoms were mediated by prenatal depressive symptoms. However, as the effect size proportions mediated were 52.2%–88.0% for the different PRSs, other mediating factors may also play a role. Interactions between the PRSs and prenatal depressive symptoms were not significantly associated with postpartum depressive symptoms. Thus, the genetic risk of prenatal depressive symptoms accounted for and did not moderate the genetic risk of postpartum depressive symptoms. This finding reflects that depressive symptoms were highly stable throughout the perinatal period.

One previous study has investigated the associations between PRSs for MDD and BD and depression during the perinatal period (Byrne et al., 2014). In this study the PRS for BD, but not MDD, was associated with PPD. Our findings are discrepant with this study; there are several possible explanations. First, the earlier study focused on PPD instead of the entire perinatal period. Second, our study used different depression outcomes. While we used depressive symptoms as a continuous variable measured with a questionnaire, the prior study predicted case/control status measured using methods including questionnaires, retrospective reports and clinical interviews in the studied cohortsIndeed, the authors noted that differences in case ascertainment methods may have influenced their findings. Third, the discrepancy may be related to differences in the measures of polygenic risk between our studies. The earlier study used polygenic profile scores (Purcell et al., 2009), and used risk scores for MDD and BD from different discovery samples than ours. Fourth, ethnic differences may explain the discrepancies, as our study was conducted in a homogenous Finnish cohort, and the prior study combined British, Dutch, Swedish, and Australian samples (Byrne et al., 2014).

Recent studies have investigated the polygenic prediction of MDD (Halldorsdottir et al., 2019; Musliner et al., 2019) and BD and SCZ (Musliner et al., 2019) using PRSs calculated using the same GWAS summary statistics as we did (Ripke et al., 2014; Ruderfer et al., 2018; Wray et al., 2018). While these studies were conducted outside the perinatal period, they are relevant due to the partially shared genetic component among the different disorders (Cross-Disorder Group of the Psychiatric Genomics et al., 2013; Lee et al., 2019; Viktorin et al., 2016), risk factors and biological mechanisms of vulnerability (Roy & Campbell, 2013; Schiller et al, 2015; Serati, Redaelli, Buoli, & Altamura, 2016; Yim et al., 2015). These studies found that PRSs for MDD2018 predicted the risk of MDD in adolescents (Halldorsdottir et al., 2019) and MDD2018, SCZ2014 and BD2018 predicted the risk of MDD in children and adults (Musliner et al., 2019), though the PRS for BD2018 predicted the

smallest increases in hazard ratios. These findings partially agree with and partially conflict with ours, though our study differs in depression phenotype and age, and was restricted to perinatal women. Ethnic differences may also explain why the PRSs for BD were not associated with depressive symptoms in our study. Alternatively, since the PRS for BD2018 predicted smaller increases in hazard ratios for than MDD2018 and SCZ2014 in the previous study (Musliner et al., 2019), it is possible that significant associations could be found in samples larger than ours. While our findings provide important evidence of the shared genetic components between perinatal depression and other psychiatric disorders, further studies are warranted to elucidate the relationships between their respective genetic bases.

The strengths of this study include prospective design, multiple measurements of depressive symptoms during pregnancy and after delivery, and a well-characterized sample with data available on multiple important covariates. Also, as most of the genotyped samples had data on depressive symptoms available during pregnancy and after delivery, sample attrition is unlikely to have influenced our findings. The limitations include the lack of measurement of depressive symptoms before pregnancy, and relatively modest statistical power to detect genetic effects. Also, the comparability of our findings to studies using diagnoses of depressive disorders and conducted in populations with different characteristics and ethnicities is limited. Furthermore, our PRSs do not account for gene–environment interactions, as they were based on summary statistics from GWASs investigating main effects.

5 | CONCLUSIONS

We found that two different PRSs for MDD and SCZ and PRS for CD, but not two PRSs for BD, were associated with prenatal and postpartum depressive symptoms. We also found that the associations between the PRSs and postpartum symptomatology were accounted for, and hence mediated prenatal depressive symptoms and that the PRSs predicted persistently high depressive symptoms throughout the perinatal period. Our study is consistent with the earlier findings suggesting that perinatal and nonperinatal depressive symptoms (Viktorin et al., 2016), and MDD (Viktorin et al., 2016), and SCZ (Cross-Disorder Group of the Psychiatric Genomics et al., 2013; Lee et al., 2019) in non-perinatal populations, have a partially shared genetic basis, and suggests that PRSs for MDD, SCZ, and CD may afford to identify women at increased risk of perinatal depression for timely preventive interventions.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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